Comprehensive Pediatric Human Immunodeficiency Virus Care and Treatment in Constanta, Romania

Implementation of a Program of Highly Active Antiretroviral Therapy in a Resource-Poor Setting

Mark W. Kline, MD, Rodica F. Matusa, MD, Letitia Copaciu, MD, Nancy R. Calles, BSN, RN, Nancy E. Kline, PhD, RN, CPNP, FAAN, and Heidi L. Schwarzwald, MD

Background: Relatively few human immunodeficiency virus (HIV)-infected children worldwide have access to care and treatment. The Romanian-American Children's Center, a collaborative project of a U.S. health care institution and the Romanian government, has established a comprehensive program of highly active antiretroviral therapy for children in Constanta, Romania.

Objectives: To describe the design and outcomes of a program of pediatric HIV/acquired immunodeficiency syndrome (AIDS) care and treatment in a resource-poor setting.

Setting: Outpatient center providing comprehensive primary and HIV/AIDS specialty care and treatment to all known HIV-infected children living in Constanta County, Romania.

Outcomes: As of August 2003, a total of 452 children were receiving highly active antiretroviral therapy. Therapy has been well-tolerated, with ~90% of children continuing to receive treatment after a median duration of follow-up of 67 weeks. Normal weight and height growth velocities have been observed among treated children. Marked decreases have been observed in rates of hospitalization and mortality. The mean change in $CD4^+$ lymphocyte count for 173 children who have both a baseline count and at least 1 follow-up count is +284 cells/μL ($P < 0.0001$).

Conclusions: Highly active antiretroviral therapy can be administered safely and effectively to children in a resource-poor setting, with outcomes comparable with those observed in U.S. pediatric antiretroviral clinical trials.

Key Words: human immunodeficiency virus infection, antiretroviral therapy, Romania, infant or child

(*Pediatr Infect Dis J* 2004;23: 695–700)

Through the end of 2002, Romania had reported 9936 pediatric HIV/AIDS cases, representing over one-half of all European pediatric HIV/AIDS cases.[1] Unique among nations worldwide, children represent 80% of all Romanian HIV/AIDS cases.

Several disastrous policies of the communist government of Nicolae Ceausescu catalyzed the Romanian pediatric HIV/AIDS epidemic. Prohibition of contraception, abortion and sex education in an attempt to encourage population growth led to large numbers of unwanted pregnancies and abandoned children. Government economic policies led to a huge increase in foreign debt and declining living standards. By the late 1980s, thousands of poor and abandoned children suffered from anemia and malnutrition, and it was common practice in hospitals and orphanages to administer vitamin injections and transfuse whole human blood unscreened for HIV, often by reuse of disposable needles. As a result, thousands of children were infected with HIV and other blood-borne pathogens.

Baylor College of Medicine, Texas Children's Hospital, the Municipal Hospital Constanta (subsequently renamed the Infectious Diseases Hospital Constanta) and the Romanian Ministry of Health and Family have worked collaboratively on a comprehensive program of pediatric HIV/AIDS care and treatment, health professional education and training and clinical research in Constanta since 1996, culminating in

Accepted for publication April 5, 2004.

From the Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX; and the Centrul de Copii Romano-American (Romanian-American Children's Center), Constanta, Romania

Supported in part by the Abbott Laboratories Fund Step Forward program, the Sisters of Charity of the Incarnate Word, the Bristol-Myers Squibb Foundation, the U.S. Agency for International Development (Baylor grant 186-A-00-00-00113), the Fogarty International Center of the U.S. National Institutes of Health (Baylor AIDS International Training and Research Program grant 5 D43 TW01036) and the National Institute of Allergy and Infectious Diseases (Baylor Center for AIDS research grant AI36211).

Address for reprints: Mark W. Kline, MD, Department of Pediatrics, Baylor College of Medicine, 6621 Fannin Street, CCC1570, Houston, Texas 77030. Fax 832-825-1281; E-mail mkline@texaschildrenshospital.org

ISSN: 0891-3668/04/2308-0695
DOI: 10.1097/01.inf.0000135454.46188.83

the construction and opening of the Centrul de Copii Romano-American (Romanian-American Children's Center) in April 2001 and the implementation of a program of highly active antiretroviral therapy (HAART) shortly thereafter. We report on the design and outcomes of this comprehensive program.

BACKGROUND

Current State of Health Care and HIV/AIDS Care and Treatment in Romania. Romania, with a total population of 22.4 million, has a per capita gross domestic product of $6475. This gross domestic product is comparable with that of Botswana ($6014) and Thailand ($6481), but substantially less than that of South Africa ($7555).[2] Romania's total health expenditure per capita ($190) is substantially less than that of Botswana ($358), Thailand ($237) or South Africa ($663). Romania has a national HIV/AIDS policy and treatment program. More than 4000 HIV-infected children and adults currently are under treatment with antiretroviral drugs, but problems with drug procurement and supply have led to frequent interruptions in treatment. It is estimated that at least 1000 more HIV-infected persons should be receiving antiretroviral treatment.[3] Between 5000 and 7000 Romanian children currently are living with HIV/AIDS.[1]

Constanta County. The judet (county) of Constanta is located in far southeastern Romania. It is a large county, measuring ~100 km in both north-south and east-west dimensions. The county has a total population of 715,172 persons, approximately two-thirds of whom reside in urban areas. The city of Constanta (population 310,526) is an important Black Sea commercial port.

Constanta is the epicenter of HIV/AIDS in Romania, with a greater number of cases than any other county. A total of 1718 cases of AIDS have been reported from Constanta county, 1529 (89%) among children. Currently there are ~620 known HIV-infected children living in Constanta county. Nine separate residential facilities house a total of ~200 orphaned or abandoned HIV-infected children; most of the other known HIV-infected children live with parents or other biologic relatives.

History of Baylor College of Medicine's Activities in Romania. The Baylor International Pediatric AIDS Initiative (www.bayloraids.org) at Baylor College of Medicine (Houston, TX) began working in Romania in 1996 under a collaborative agreement with the Romanian Ministry of Health and Family, signed by then Minister of Health Ms. Daniela Bartos and Dr. Ralph D. Feigin, Baylor's President and Chief Executive Officer. Baylor's initial activities in Romania focused on health professional education and training, including sponsorship of conferences and workshops on pediatric HIV/AIDS for Romanian physicians and nurses and a bidirectional short term (1 or 2 months) physician exchange program. These activities soon expanded with the development of a collaborative partnership between Baylor and the Municipal Hospital Constanta. Under a Memorandum of Agreement between the 2 institutions, professionals from Baylor provided assistance with pediatric HIV/AIDS patient care. A longitudinal study was begun to track the health status and outcomes of HIV-infected children in care at the hospital,[4] a collaborative oral health program was established and a computerized patient database was created,[5] all as a prelude to instituting a program of pediatric HAART.

Centrul de Copii Romano-American (Romanian-American Children's Center). As collaborative activities in Constanta grew, Baylor began investigating the possibility of establishing a dedicated facility for pediatric HIV/AIDS care and treatment, health professional training and clinical research. The Municipal Hospital Constanta made available for this purpose an abandoned orphanage located about 3 km from the hospital in a residential neighborhood in the city of Constanta. The building was in an extreme state of disrepair and had been thoroughly vandalized (Fig. 1), but a U.S. architectural and engineering team attested to its structural integrity. Renovation of the building was completed, and the Romanian-American Children's Center opened officially on April 6, 2001. All known HIV-infected children residing in Constanta county transferred their care to the center at that time. The center has 3 outpatient examination rooms, a dental examination and treatment room, a small laboratory, 2 inpatient observation and procedure rooms, a multipurpose computer and play room for children, a library, a large conference room, locked rooms containing cabinets and refrigerators for storage of medications, staff offices and a 2-bedroom apartment for visiting health professionals (Figs. 2 and 3).

Approximately 620 children currently receive care at the Romanian-American Children's Center, representing one of the largest concentrations of HIV-infected children in care in any center worldwide. An average of 600 outpatient visits are recorded each month. Routine laboratory studies are performed at the Infectious Diseases Hospital Constanta; $CD4^+$ lymphocyte measurements are done on site at the center by flow cytometry, and plasma HIV RNA measurements are performed at Baylor's Center for AIDS Research International Core Laboratory in Bucharest. The center has a full time Romanian professional staff of 37, including 6 infectious disease specialists and pediatricians. Professionals from Baylor work at the center on an intermittent basis.

DESIGN OF THE ANTIRETROVIRAL TREATMENT PROGRAM

Drug Access and Accountability. Drug procurement, management and accountability were considered a prerequisite to establishment of a program of pediatric HAART. At the time the Romanian-American Children's Center was opened, key

FIGURE 1. An abandoned orphanage was renovated to establish the Romanian-American Children's Center.

FIGURE 2. Exterior view of the Romanian-American Children's Center.

staff were hired, and controls and protections were put in place to ensure against loss or diversion of antiretroviral drugs. All drugs are stored in locked rooms at the center. Only the clinic head nurse has key access to these rooms. A daily ledger is kept of all drugs dispensed to individual patients. This ledger is reconciled on a daily basis with the number of bottles of medication remaining in stock. All of this information is entered daily into a computerized database created expressly for this purpose. On any given day, it is possible to query the database and determine the precise number of bottles of each formulation of each antiretroviral medication in stock at the center. Medications are reordered when supplies reach a predetermined minimum.

The Romanian government purchases antiretroviral drugs for HIV-infected children and adults. However, procurement irregularities and limitations of available funding have led in the past to frequent interruptions of therapy. After the Romanian-American Children's Center opened, 2 phar-

FIGURE 3. Outpatient clinic area of the Romanian-American Children's Center.

maceutical companies agreed to donate antiretroviral drugs in perpetuity for up to 500 children in care at the center. The drugs are donated to Baylor and are shipped from the United States to Romania periodically. On a value basis, donated drugs constitute 75% of all drugs dispensed at the Romanian-American Children's Center.

CRITERIA FOR TREATMENT AND DRUG ADMINISTRATION

Children are being treated with HAART in an open manner, by prescription, according to package insert instructions. Children in any U.S. Centers for Disease Control and Prevention (CDC)[6] category other than N1 or A1 are considered eligible for treatment. Children already receiving antiretroviral therapy are considered eligible for a change to HAART if they have evidence of clinical, virologic and immunologic HIV disease progression.

Lopinavir-containing HAART is being used preferentially at the Romanian-American Children's Center. Drugs used in combination with lopinavir are being chosen on the basis of patient treatment history; genotyping for resistance mutations is not being performed. Every child is naive to lopinavir and to at least one other agent that is being used in combination. Children may have been treated previously with other HIV protease inhibitors.

All antiretroviral medications are stored according to package insert instructions. Weight and body surface area are determined every 4 weeks, and the drug dose is changed when indicated by an increase or decrease in weight. Adherence is monitored by measuring or counting returned medication and by questioning the parent and/or child at each scheduled clinic visit.

Patients receive prophylaxis for *Pneumocystis carinii* pneumonia according to established guidelines,[7] and nutritional support and antibiotic therapy are prescribed as needed. Immunomodulators (excluding corticosteroids and intravenous immunoglobulin) are not used.

Patient and Family Education and Support. All children and caregivers are counseled initially and monthly regarding the importance of medication adherence. At the time HAART is initiated, each child and family is given a 1-page, individualized reference sheet that shows actual size color photographs of the pills they will be taking, together with dosing instructions and any other special instructions (eg, diet). Medication boxes are provided, and each family is instructed in their correct use. An illustrated 20-page Romanian language booklet on HIV/AIDS and antiretroviral therapy was created for use at the center and is given to each family as an adjunct to verbal counseling. This booklet contains a glossary of key terms and is written at a sixth or seventh grade educational level. A mobile, multidisciplinary medical/psychosocial team visits children and families in the community ~5 days each week. This enables center staff to monitor antiretroviral medication storage, administration and adherence as well as to assess the impact of factors in the home and family on treatment. Five separate parent-led support groups meet on a monthly basis with members of the health care team. These meetings provide a forum for discussion of a variety of medical, psychosocial and other issues and are a source of support for families coping with the care of chronically ill children.

Clinical and Laboratory Monitoring. All treated children are being evaluated clinically and with routine laboratory tests on a monthly basis. Because of cost considerations, $CD4^+$ lym-

phocyte counts and plasma HIV RNA measurements (Roche Molecular Systems, Branchburg, NJ) are being obtained at baseline and intervals of ~6 months only on a subset of treated children.

OUTCOMES

As of August 2003, a total of 452 children were receiving HAART at the Romanian-American Children's Center. Highly active antiretroviral therapy has been well-tolerated, with ~90% of children remaining on treatment after a median duration of follow-up of 67 weeks. Two hundred nineteen children have had weight and height measurements at baseline and again at least 6 months after beginning HAART. One hundred twenty-two (56%) and 142 (65%) children, respectively, had baseline weights and heights less than the 5th percentile for age and gender.[8] After at least 6 months of HAART, the median weight growth velocity for the group as a whole is at the 25-50th percentile; 196 (89%) of 219 children have weight growth velocities greater than the 10th percentile. The median height growth velocity for the group as a whole is at the 50-75th percentile; height growth velocity is greater than the 10th percentile in every case.[9]

All HIV-infected children requiring hospitalization in Constanta county are admitted to the Infectious Diseases Hospital Constanta for care and treatment. The average daily census on the pediatric HIV/AIDS unit at that hospital has declined from ~30 in 2001 to ~4 during the 6-month period ending July 31, 2003. Fourteen deaths have occurred among children receiving HAART. None of these deaths was thought to be related in any way to antiretroviral therapy. Most of the deaths occurred among children with advanced HIV disease at the time HAART was initiated; 9 of the 14 deaths occurred within 12 weeks of starting HAART. The annualized mortality rate we have observed among children treated with HAART (3%) compares favorably with the annual mortality rates we observed in a cohort of HIV-infected children followed prospectively in Constanta during 4 years ending May 2002 (19, 9, 8 and 14%, respectively).[4]

Only 35 children have had plasma HIV RNA concentrations measured both at baseline and after at least 12 weeks of HAART. Twenty (57%) of these 35 children have on-treatment plasma HIV RNA concentrations of <400 copies/mL. The mean change in $CD4^+$ lymphocyte count for the 173 children, who have both a baseline count and at least one follow-up count is +284 cells/μL ($P < 0.0001$).

DISCUSSION

It is estimated that 2.5 million children were living with HIV/AIDS at the end of 2003, most in the developing world.[10] Eastern Europe has the world's fastest growing HIV/AIDS epidemic, with about 250,000 adults and children newly infected with HIV in 2003 alone.

Therapy for HIV-infected adults and children living in the world's poor countries has been limited not only by expense but also by lack of infrastructure and human capacity for delivering HIV/AIDS care and treatment. We describe the creation of a program in Constanta, Romania designed to deliver state-of-the-art, comprehensive pediatric HIV/AIDS care and treatment. This program is a collaborative partnership between a private U.S. academic institution, a Romanian health care institution and the Romanian government, with support from corporate and private foundations, a faith-based organization and the U.S. government. Highly active antiretroviral therapy is made possible by a Romanian government program, supplemented by donations from 2 large pharmaceutical companies.

Four hundred fifty-two children have started HAART at the Romanian-American Children's Center since November 1, 2001. We believe this may be the largest number of children treated with HAART in any single center worldwide. In general, therapy has been administered safely and effectively.

More than one-half of the children treated with HAART had baseline weight and/or height measurements less than the 5th percentile for age and gender, reflecting advanced HIV disease, but growth velocities have improved greatly with treatment. Growth velocity is a useful predictor of survival in HIV-infected children.[11,12] Rates of hospitalization and death are much lower than those observed in earlier years in the same population. Marked improvement in $CD4^+$ lymphocyte counts has been observed, and more than one-half of a small number of children tested 12 weeks or more after treatment initiation have plasma HIV RNA concentrations of <400 copies/mL, results comparable with those recently reported from a multicenter clinical trial of 100 children treated with lopinavir-containing HAART.[13]

The care and treatment program of the Romanian-American Children's Center has been developed deliberately, with careful consideration of the most efficient use of limited resources. Emphasis has been placed on development of human capacity and actual delivery of care and treatment, rather than on establishment of sophisticated but perhaps not completely essential capabilities (eg, antiretroviral resistance assays and routine use of plasma HIV RNA measurements). The formulation of such a center or program is likely to vary from one setting to another, depending on existing resources, capabilities and needs.

We attribute the success of this program to a variety of factors: a well-trained multidisciplinary staff; highly motivated children and caregivers; careful attention to factors influencing medication adherence; and a commitment to truly comprehensive HIV/AIDS care and treatment, including home and palliative care, psychosocial support and community education. The collaborating partners have dealt consistently with one another in an open and honest manner. Follow

through on commitments has been expected and consistently delivered.

We have demonstrated that HAART can be administered safely and effectively to children in a resource-poor setting. Funding agencies, including the U.S. government, should allocate adequate resources to rapidly scale up pediatric HIV/AIDS care and treatment in resource-poor settings worldwide. Already, Baylor , in collaboration with the government of Botswana, has opened a second such center, the Botswana-Baylor Children's Clinical Center of Excellence, in Gaborone. More than 1000 HIV-infected children were in care in the center in Botswana within 6 months of its opening on June 20, 2003. Baylor believes that such pediatric HIV/AIDS centers of excellence will be key to demystifying the care and treatment of HIV-infected children in the developing world, communicating a message of hope and optimism to communities hard hit by HIV/AIDS, destigmatizing HIV/AIDS, reducing the isolation of affected children and families and enhancing access to modern HIV/AIDS care and treatment, including HAART.

REFERENCES

1. Romanian Ministry of Health and Family. HIV/AIDS update. *FORUM Newsl.* 2002;8.
2. World Health Organization. Available at: http://www.who.int/country. Accessed February 10, 2004.
3. Novotny T, Haazen D, Adeyi O. HIV/AIDS in southeastern Europe: case studies from Bulgaria, Croatia and Romania. The World Bank, Washington, DC, February 11, 2003.
4. Kline MW, Matusa RF, Simon CL, Kline NE. Four-year longitudinal study of HIV among children in Constanta, Romania. Presented at the 40th Annual Meeting of the Infectious Diseases Society of America [abstr. 438], Chicago, 2002.
5. Kozinetz CA, Matu°a R, Cazacu A. The burden of pediatric HIV/AIDS in Constanþa, Romania: a cross-sectional study. *BMC Infect Dis*. 2001; 1:7.
6. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(RR-12):1–10.
7. Centers for Disease Control and Prevention. 1995 revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR*. 1995;44(RR-4):1–11.
8. Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr*. 1979;32:607–629.
9. Roche AF, Himes JH. Incremental growth charts. *Am J Clin Nutr*. 1980;33:2041–2052.
10. UNAIDS. AIDS epidemic update, December 2003. Available at: http://www.unaids.org. Accessed February 10, 2004.
11. McKinney RE Jr. , Robertson WR. Duke Pediatric AIDS Clinical Trials Unit: effect of human immunodeficiency virus infection on the growth of young children. *J Pediatr*. 1993;123:579–582.
12. Carey VJ, Yong FH, Frenkel LM, McKinney RE Jr. Pediatric AIDS prognosis using somatic growth velocity. *AIDS*. 1998;12:1361–1369.
13. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2003;22:216–224.